filing date of the present application is March 30, 1998. Accordingly, no petition is required and the Applicant respectfully requests entry of the amendment.

The claims are 15-19. Claim 15 has been amended to more clearly claim the invention. References to oxygen-carbon and sulfur-carbon bonds between the linker and polymer have been deleted. Since the Examiner did not receive a portion of Claim 19, the claim has been amended to include the missing portion. Dependent Claim 20 has been added by way of this amendment since it was not originally received by the Examiner. No new matter has been added by way of this amendment.

The claims, as amended, are directed to a hydrolyzable drug delivery system having an active ingredient covalently bonded to a linker, which is covalently bonded to a portion of subunits of a crosslinked polymer via a nitrogen-carbon or phosphorus-carbon bond.

Claim Rejections

Claim 15 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ebert et al., *Journal of Biomedical Materials Research*, Vol. 16, pp. 629-638, 1982 (hereinafter, "Ebert"), or Blossey et al., *Journal of Organic Chemistry*, Vol. 55, pp. 4664-4668, 1990 (hereinafter, "Blossey"), or Sarobe et al., *Polymers for Advanced Technologies*, Vol. 7, pp. 749-753, 1996 (hereinafter, "Sarobe"), or Severian et al., Chimica*oggi*, "Boactive Polymers", Vol. 58, pp. 59-63, 1988 (hereinafter, "Severian"). Claims 16-19 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over any one of Ebert, Blossey, Sarobe, or Severian, in view of U.S. Patent No. 5,827,925, to Tremont, et al. (hereinafter, "Tremont"). Applicant respectfully traverses these rejections.

The present invention is directed, to a hydrolyzable drug delivery system having an active ingredient covalently bonded to a linker which is, in turn, covalently

bonded to a portion of subunits of a crosslinked polymer via a nitrogen-carbon or phosphorus-carbon bond. None of the cited references provide any motivation to experiment with a nitrogen-carbon or phosphorus-carbon covalent bond between a linker and polymer with a reasonable expectation of success. In fact, none of the cited references even recognize the significance of the covalent bond for the sustained release of active ingredients.

Ebert discloses, *inter alia*, the immobilization of prostacyclin on a chlorosulfonated polymer via a diaminoalkane linker arm. Ebert does not disclose or suggest a delivery system for active ingredients or the possibility of a linker being bound to the polymer via a N-C or P-C bond. Rather, Ebert utilizes a N-S bond to connect the active ingredient to the polymer.

Blossey discloses, *inter alia*, the preparation of carboxyl- and hydroxyl-containing cholic acid derivatives coupled to chloromethylated polystyrene. Blossey does not disclose or suggest a delivery system for active ingredients or the possibility of a linker being bound to the polymer via a N-C or P-C bond. Rather, Blossey utilizes an ether bond to connect the active ingredient to the polymer.

Sarobe discloses, *inter alia*, systems wherein immunoglobulin G is covalently coupled to chloromethylstyrene beads at the protein's amino group. Sarobe does not disclose or suggest a delivery system for active ingredients or the possibility of a linker being bound to the polymer via a N-C or P-C bond. Rather, Sarobe reads, "[p]olystyrene beads with chloromethyl functional groups are particularly useful since further chemical derivatization procedures are merely a one-step reaction between the chloromethyl group and the amino groups in the protein molecules." The chloromethyl functional group on the polystyrene does not fall within Applicant's definition of a linker or claimed bonding sites.

Severian is directed, *inter alia*, to metronidazole coupled to an acrylic acid-styrene copolymer via condensation of the hydroxyl groups on the metronidazole with carboxyl groups on the acrylic acid copolymer. Severian does not disclose or suggest the possibility of a linker being bound to the polymer via a N-C or P-C bond.

Tremont, is directed to an impressive drug delivery system; however, Tremont does not disclose or motivate a skilled artisan to utilize the specific linker-polymer bonding, namely N-C and P-C, disclosed by the present claims. Also, Tremont favors the use of silyl linkers. Thus, Tremont does not remedy the shortcomings of Ebert, Blossey, Sarobe, or Severian.

The Examiner states, "a person skilled in the art would have found it obvious at the time the invention was made . . . since the N-C bond, . . ., as well as P-C bond formation requires less energy than C-O bond formation." If ease of bond formation was the only critical parameter of the present invention, surely at least one of the five cited references would have suggested attempting or substituting the linker-polymer bond. A suggestion and expectation of success must be found in the prior art, not in the Applicant's disclosure. None of the references disclose or suggest that N-C or P-C bonds are fungible or desirable over any other bonds. Further, the present invention contains several bonding parameters; however, none of the prior art references give any indication which parameters are critical or how to vary the several choices in order to arrive at the presently-claimed invention. No expectation of success exists where the prior art provides no guidance as to which parameter(s) to vary in order to yield the invention.

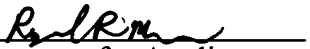
Accordingly, the Applicant respectfully submits the present invention is novel and non-obvious over the cited references and requests reconsideration and withdrawal of the rejections.

CONCLUSION

Wherefore, it is respectfully submitted the cited art, whether taken alone or together, does not disclose or suggest the presently-claimed invention. Accordingly, it is respectfully requested that the claims be allowed and the case passed to issue.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,



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Marked-Up Version to Show Specification Revisions Made

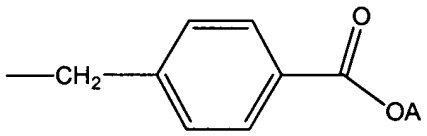
On page 1, after the title, the following paragraph was inserted.

This application claims the benefit of U.S. Provisional Application No. 60/042,641, filed April 4, 1997.

Marked-Up Version to Show Claim Revisions Made

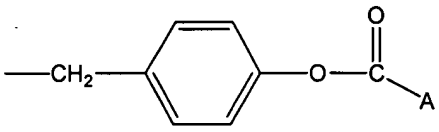
15. (AMENDED) A delivery system comprising: an active ingredient covalently bonded to a linker through a hydrolyzable covalent bond formed with a hydroxyl, CO_2H, amino, mercapto, or enolizable carbonyl moiety of the active ingredient to produce an ester, carboxylic acid, anhydride, amide, thioester, or enol ester; said linker being covalently bonded to a portion of subunits of a crosslinked polymer through a linker-polymer covalent bond selected from the group consisting of a nitrogen-carbon bond[, an oxygen-carbon bond, a sulfur-carbon bond,] and a phosphorus-carbon bond.

19. (AMENDED) The delivery system of Claim 18 wherein the active ingredient and the linker form a substituent on a 4-dimethylaminomethyl moiety or a 3-dimethylaminomethyl moiety having a structure represented by

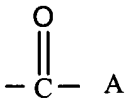


wherein OA is the covalently bonded active ingredient.

20. (NEW) The delivery system of Claim 18 wherein the active ingredient and the linker form a substituent on a 4-dimethylaminomethyl moiety or a 3-dimethylaminomethyl moiety having a structure represented by



wherein



is the covalently bonded active ingredient.